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PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53(b)(2).

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TITLE OF THE INVENTION *(280 characters max)*

Methods of Medical Treatment Using Periodic Acceleration

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ENCLOSED APPLICATION PARTS *(check all that apply)*

[x]	Specification	*Number of Pages* [11]	[]	Other *(specify):*
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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government

[x] No
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Respectfully submitted,

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METHODS OF MEDICAL TREATMENT USING PERIODIC ACCELERATION

Inventor: **Marvin A. SACKNER**

RELATED APPLICATIONS

This application hereby incorporates-by-reference U.S. Patent Application Serial Number 10/439,957 (the '957 application) which was filed on May 15, 2003.

BACKGROUND OF THE INVENTION

The background for the present application is substantially the specification of the '957 application.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide medical treatments based on the periodic acceleration of the subject's body, where said periodic acceleration causes the external addition of pulses to the tissues of the subject, as described in the '957 application.

The presently preferred medical treatments possible with externally applied periodic acceleration according to the present invention include the treatment of cancer, and the preconditioning, conditioning, and/or postconditioning of subjects, particularly athletes, to prevent and/or treat prevent/treat any of the insalubrious conditions which may be caused by athletic activity, whether such activity is continuous, periodic, or intermittent.

DETAILED DESCRIPTION OF THE PRESENTLY PREFERRED EMBODIMENTS

The present invention relates to both an apparatus and methods of treatment using the apparatus. The following text, in which the presently preferred embodiments are described, should be understood within the context of the '957 application. Further information, including the construction and use of an exemplary device to provide periodic acceleration, may be found in the '957 application.

Periodic Acceleration for the Treatment of Cancer

(The following pertains to paragraph [0043] in the '957 application)

Tumors in which nuclear factor kappa beta is present in the nucleus of cells (constitutive activation) include the following:

B cell lymphoma;
Hodgkin's disease;
T cell lymphoma;
adult T cell lymphoma;
acute lymphoblastic leukemia;
breast cancer;
thyroid cancer;
pancreatic cancer;
prostate cancer;
melanoma;
head and neck squamous cell carcinoma;
colon cancer;
multiple myeloma;
ovarian cancer;
bladder cancer; and
lung cancer (Garg A, Aggarwal B B. *Nuclear transcription factor-kappa B as a target for cancer drug development*. Leukemia, 16:1053-68 (2002)).

Tumorigenesis is characterized by self-sufficiency in growth signals, insensitivity to growth inhibition, evasion of apoptosis, immortalization, sustained angiogenesis, tissue invasion and metastasis. (Hanahan D, Weinberg R A. *The hallmarks of cancer*, Cell, 100:57-70 (2000)). Nuclear factor kappa beta that is constitutively activated in tumor cells promotes tumorigenesis since this gene produces negative feedback of nuclear factor kappa beta, causes cancer cell proliferation, prevents apoptosis (programmed cell death), increases angiogenesis, and increases metastatic potential. (Garg A, Aggarwal B B. *Nuclear transcription factor-kappa B as a target for cancer drug development*. Leukemia, 16:1053-68 (2002); Bharti A C, Aggarwal B B. *Nuclear factor-kappa B and cancer: its role in prevention and therapy*. Biochem.Pharmacol., 64:883-88 (2002)). Because of these factors, Karin suggested that nuclear factor kappa beta should receive as much attention from cancer researchers as it has already from immunologists (Karin M, Cao Y, Greten F R, Li Z W. *NF-kappaB in cancer: from innocent bystander to major culprit*, Nat.Rev.Cancer, 2:301-10 (2002)).

Indeed, pharmacologic agents that block nuclear factor kappa beta activity have been employed to treat cancerous cell lines with success (Fujioka S, Sclabas GM, Schmidt C, Niu J, Frederick WA, Dong QG et al. *Inhibition of constitutive NF-kappa B activity by I kappa B alpha M suppresses tumorigenesis*, Oncogene 22:1365-70 (2003); Liptay S, Weber CK, Ludwig L, Wagner M, Adler G, Schmid R M. *Mitogenic and antiapoptotic role of constitutive NF-kappaB/Rel activity in pancreatic cancer*. Int.J.Cancer,105:735-46 (2003); Umezawa K, Ariga A, Matsumoto N. *Naturally occurring and synthetic inhibitors of NF-kappaB functions*, Anticancer Drug Des.,15:239-44 (2000))

However, the problem in human cancers is distribution of the pharmacological agent to the tumor and toxicity to normal cells. Nitric oxide released from eNOS with periodic acceleration offers a non-toxic means to suppress activated nuclear factor kappa beta (Stefano GB, Prevot V, Cadet P, Dardik I. *Vascular pulsations stimulating nitric oxide release during cyclic exercise may benefit health: a molecular approach (review)*, Int.J.Mol.Med., 7:119-29 (2001)). Further, since tumors are characterized by a well-developed blood supply, distribution of the nitric oxide suppressant activity on activated nuclear factor kappa beta in not an issue.

Thus, periodic acceleration alone or in conjunction with chemotherapeutic or x-ray or other cancer suppressing agents or technology offers a way to treat cancers. Furthermore, application of periodic acceleration either alone or with other preventative agents can be used to prevent cancers.

Periodic Acceleration for Preconditioning and/or Conditioning

[The following pertains to paragraph [0068] in the '957 application]

Stretch-induced muscle injuries or strains, muscle contusions and delayed-onset muscle soreness (DOMS) are common muscle problems in athletes. Anti-inflammatory treatment is often used for the pain and disability associated with these injuries. The most recent studies on nonsteroidal anti-inflammatory drugs (NSAIDs) in strains and contusions suggest that the use of NSAIDs can result in a modest inhibition of the initial inflammatory response and its symptoms. However, this may be associated with some small negative effects later in the healing phase. Corticosteroids have generally been shown to adversely affect the healing of these acute injuries. The effect of NSAIDs on DOMS appears small at best (Almekinders L C. *Anti-inflammatory treatment of muscular injuries in sport. An update of recent studies*, Sports Med., 28:383-88 (1999)). Prolonged and strenuous exercise induces significant increases in plasma IL-1beta, IL-6 and tumor necrosis factor alpha (Brenner I K, Natale V M, Vasiliou P, Moldoveanu A I, Shek P N, Shephard R J. *Impact of three different types of exercise on components of the inflammatory response*, Eur. J. Appl. Physiol. Occup. Physiol., 80:452-60 (1999); Bruunsgaard H, Galbo H, Halkjaer-Kristensen J, Johansen T L, MacLean D A, Pedersen B K. *Exercise-induced increase in serum interleukin-6 in humans is related to muscle damage*, J. Physiol, 499 (Pt 3):833-41 (1997); Pedersen B K, Ostrowski K, Rohde T, Bruunsgaard H. *The cytokine response to strenuous exercise*. Can. J. Physiol. Pharmacol., 76:505-11 (1998)).

There is a positive correlation between elevated serum IL-6 levels and skeletal muscle damage in terms of creatine kinase elevations (Bruunsgaard H, Galbo H, Halkjaer-Kristensen J, Johansen T L, MacLean D A, Pedersen B K. *Exercise-induced increase in serum interleukin-6 in humans is related to muscle damage*, J. Physiol, 499 (Pt 3):833-41 (1997)). In football players who require intravenous hydration for muscle cramps after training sessions, all have extremely high levels of serum nitrite, presumably released from iNOS as a result of the stress of strenuous exercise (Maddali S, Rodeo S A, Barnes R, Warren R F, Murrell G A. *Postexercise increase in nitric oxide in football players with muscle cramps*. Am. J. Sports Med., 26:820-24 (1998)). Athletes seem to be more prone to upper respiratory viral infections probably because strenuous exercise promotes increase of IL-6, tumor necrosis factor alpha, and large quantities of nitric oxide that compromise the immune defense system. These infections usually appear after exercise discontinuation (within 3 days) particularly in those athletes practicing sports that

require a long term effort and resistance (Gani F, Passalacqua G, Senna G, Mosca F M. *Sport, immune system and respiratory infections*, Allerg. Immunol.(Paris), 35:41-46 (2003)).

Small quantities of nitric oxide suppress strenuous exercise induced activation of nuclear factor kappa beta thereby diminishing IL-1beta, IL-6, tumor necrosis factor and other inflammatory cytokines and adhesion molecules. In addition, small quantities of nitric oxide from eNOS suppress activity of iNOS (Stefano GB, Prevot V, Cadet P, Dardik I. *Vascular pulsations stimulating nitric oxide release during cyclic exercise may benefit health: a molecular approach (review)*. Int. J. Mol. Med., 7:119-29 (2001)).

Therefore, periodic acceleration can mitigate skeletal muscular cramps during an athletic event, and help to prevent muscle strains during an event as well as delayed onset muscular soreness (DOMS) and involuntary muscle cramps and spasms immediately following the athletic event and delayed until the sleeping hours.

In addition to skeletal muscle damage and propensity to viral infections associated with strenuous exercise, damage to heart muscle may occur even in normal subjects. Cardiac troponin T (cTnT) and troponin I (cTnI) are highly sensitive and specific for detecting myocardial damage even in the presence of skeletal muscle injury. Ultraendurance exercise may cause myocardial damage as indicated by elevations of these biochemical cardiac-specific markers and also by echocardiography (Rifai N, Douglas P S, O'Toole M, Rimm E, Ginsburg G S. *Cardiac troponin T and I, echocardiographic [correction of electrocardiographic] wall motion analyses, and ejection fractions in athletes participating in the Hawaii Ironman Triathlon*, Am. J. Cardiol., 83:1085-89 (1999); Shave RE, Dawson E, Whyte G, George K, Ball D, Gaze D C *et al. Evidence of exercise-induced cardiac dysfunction and elevated cTnT in separate cohorts competing in an ultra-endurance mountain marathon race*,. Int. J. Sports Med., 23:489-94 (2002); Ohba H, Takada H, Musha H, Nagashima J, Mori N, Awaya T *et al. Effects of prolonged strenuous exercise on plasma levels of atrial natriuretic peptide and brain natriuretic peptide in healthy men.* Am. Heart J., 141:751-58 (2001)). There are no studies reported in the literature on normal subjects with regard to less strenuous exercise but it stands to reason that in some individuals, minor damage might occur. Minimal myocardial damage could compromise athletic performance.

Activation of eNOS to release small quantities of nitric oxide preconditions the heart against the adverse effects of compromising the blood supply to the heart that produces myocardial damage. Periodic acceleration activates eNOS through increased pulsatile shear stress and, as such, is a means to

precondition the heart. Endogenous nitric oxide 1) reduces myocardial oxygen consumption and thus improves regional myocardial function for any given level of myocardial blood flow, oxygen consumption and energetics, 2) preserves contractile calcium sensitivity during myocardial ischemia, and 3) contributes to hibernation, i.e., adaptation to myocardial ischemia, by preserving regional contractile function without any effect on myocardial energetics (Heusch G, Post H, Michel MC, Kelm M, Schulz R. *Endogenous nitric oxide and myocardial adaptation to ischemia*. Circ. Res., 87:146-52 (2000)). Since the limitation to athletic activities often is the amount of blood pumped by the heart through the body, preconditioning with periodic acceleration serves to optimize athletic performance.

Exercise-induced bronchospasm (EIB), i.e., an asthmatic episode, affects up to 35% of athletes and up to 90% of asthmatics (Kukafka DS, Lang DM, Porter S, Rogers J, Ciccolella D, Polansky M *et al. Exercise-induced bronchospasm in high school athletes via a free running test: incidence and epidemiology*. Chest, 114:1613-22 (1998)). This factor limits athletic capabilities.

Since many athletic venues do not permit effective drugs for the treatment of asthma because of they also improve performance unrelated to alleviation of asthma, pretreatment of such athletes can be accomplished with periodic acceleration to prevent exercise induced asthma. Here, the beneficial agent, nitric oxide is generated from the athlete's own body.

CONCLUSION

According to one aspect of the present invention, periodic acceleration is used to either treat or prevent cancers in human tissues. The inventive treatment may either be a stand-alone method or used in conjunction with other therapeutic or preventative modalities.

In one embodiment, the periodic acceleration provided by a motion platform to a patient causes release of nitric oxide from the vascular endothelium of the patient through activation of endothelial nitric oxide synthase (eNOS) which in turn suppresses nuclear factor kappa beta. The suppression of nuclear factor kappa beta will treats or prevents cancer at least because nuclear factor kappa beta, which is constitutively activated in tumor cells, promotes tumorigenesis, causes cancer cell proliferation, prevents apoptosis (programmed cell death), increases angiogenesis, and increases metastatic potential. There may be other effects caused by the periodic acceleration which aid in the treatment and prevention of cancer.

According to another aspect of the present invention, treatment using periodic acceleration is used for one of preconditioning, conditioning, or postconditioning an athlete. In other words, treatment with periodic acceleration before, during, or after athletic performance, or regular treatment with periodic acceleration as a regimen for the athlete, may prevent and/or treat tissue damage, reduce systemic stress, increase athletic performance, and/or prevent/treat any of the problems caused by strenuous athletic activity, whether such activity is continuous, periodic, or intermittent. The inventive treatment may either be a stand-alone method or used in conjunction with other therapeutic or preventative modalities.

In one embodiment, pretreatment with periodic acceleration improves athletic performance by preconditioning any body tissue of the athlete. Such body tissues include, but are not limited to, the heart, lungs, muscular tissue, skeletal tissue, etc. As one example, preconditioning the heart by periodic acceleration treatment may prevent myocardial damage and/or optimize athletic performance by improving cardiac function through activation of eNOS.

In one embodiment, pretreatment with periodic acceleration mitigates skeletal muscular cramps during an athletic event and helps prevent muscle strains during an event as well as delayed onset muscular soreness (DOMS) and involuntary muscle cramps and spasms immediately following the athletic event and/or delayed until the sleeping hours.

In one embodiment, pretreatment with periodic acceleration is used to treat exercise-induced bronchospasm in an athlete. Such pretreatment of susceptible individuals leads to improved athletic performance.

In one embodiment, pretreatment with periodic acceleration helps to reduce and/or prevent susceptibility of athletes to viral and bacterial infections.

In one embodiment, treatment using periodic acceleration assists or replaces the use of corticosteroids and non-steriodal anti-inflammatory drugs (NSAIDs) in management of pain, injury, muscle soreness, strains, and contusions in athletes.

In one embodiment, repeated treatments of periodic acceleration provides cumulative effectiveness in the treatment of athletes.

In one embodiment, the provided periodic acceleration causes release of nitric oxide from the vascular endothelium through activation of endothelial nitric oxide synthase (eNOS) that in turn scavenges reactive oxygen species thereby diminishing or eliminating oxidative stress. This, in turn, treats and prevents conditions that have oxidative stress as a major component..

In one embodiment, pretreatment, treatment, and/or post-treatment with periodic acceleration treats or prevents cramps, aches, soreness, spasms, and other maladies brought on by exercise and/or other athletic activity. In this and other embodiments, the periodic acceleration provided by a motion platform to a patient causes release of nitric oxide from the vascular endothelium of the patient through activation of endothelial nitric oxide synthase (eNOS) which in turn suppresses nuclear factor kappa beta

and the activity of iNOS. The suppression of nuclear factor kappa beta treats or prevents cramps, aches, soreness, spasms, and the like at least because the suppression of nuclear factor kappa beta diminishes IL-1beta, IL-6, tumor necrosis factor and other inflammatory cytokines and adhesion molecules. The suppression of iNOS activity may treat or prevent cramps, aches, soreness, spasms, and the like at least because the suppression of iNOS may diminish IL-1beta, IL-6, tumor necrosis factor and other inflammatory cytokines and adhesion molecules. There may be other effects caused by the periodic acceleration which aid in the treatment and prevention of cramps, aches, soreness, spasms, and the like.

The apparatus for, and/or method of, providing periodic acceleration may take many forms. The following is an example of an device for providing periodic acceleration to an athlete/subject, and the present invention is not limited, in any way, shape, or form, by this example: an exemplary motion platform for providing periodic acceleration for medical treatments according to the present invention comprises:

a box frame providing a foundation of the motion platform;

a drive module adjoining the box frame and operably movable relative to the box frame; and

a support connected to the drive module and comprising:

a planar surface for supporting the subject, and having a head end and a foot end; and

a footboard connected at the foot end of the planar surface, where the footboard rises perpendicularly to the planar surface and has cast shoes for securing the feet of the subject to the support.

The drive module provides periodic acceleration to the patient by moving in a line parallel to the planar surface of the support while the subject is secured to the support by the cast shoes on the footboard. The periodic acceleration is alternately in the direction of the head end, and the foot end, of the planar surface, whereby the motion platform adds pulses to the fluid filled channels of the subject's body.

In one embodiment of such an motion platform, the box frame has four wheel tracks located near the four corners of the top portion of the box frame, and the drive module has four corresponding track wheels at corresponding locations on the top portion of the drive module. The track wheels extend from the

top portion of the drive module and rest in the wheel tracks of the box frame, whereby the drive module sits within the box frame and is operably movable relative to the box frame.

In one embodiment of such a motion platform, the drive module has a frame with a head end and a foot end. Within the drive module are a head end and a foot end pair of counterweights. Each pair of counterweights is attached to the frame by a drive shaft around which rotate first and second counterweights which share a plane of rotation, wherein the first counterweight rotates in an opposite direction of the second counterweight such that their centrifugal forces cancel each other except in the direction of the head end and the foot end of the frame. By rotating the pair counterweights, a periodic acceleration is alternately induced in the direction of the head end, and the foot end, of the planar surface of the support.

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